

Preclinical Safety Studies for the Development of Tumor Vaccines

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Tumor Vaccine Strategies I

- Autologous or allogeneic tumor cells
 - Modified (chemical, gene, etc) or unmodified
- Tumor-associated antigens (TAA) \pm adjuvant
 - Recombinant, from lysate, other
 - Modified or native
- APC (with and without TAA loading)
 - Modified (cell fusion, gene, etc) or unmodified

Tumor Vaccine Strategies II

- Gene-based TAA \pm adjuvant
- Recombinant virus (oncolytic, non-oncolytic)
- Adoptive cellular therapies (T, NK, other)
- Cytokine therapies
- Other

Special Challenges for Tumor Vaccine Preclinical Development

- Few relevant animal models
 - Utility of homologous models
- Species specificity
 - Immunogen and “Vehicles”
 - Immune response
- Unconventional PK/PD/TK relationships
- Overcoming self-tolerance
- Durability and spectrum of protection



Goals of the Preclinical Safety Program I

- To recommend an initial safe starting dose and dose regimen in human subjects
 - Safety is a function of each component of the vaccine and the interaction of the components
 - Preclinical studies should help to define:
 - dose/activity relationship
 - dose/toxicity relationship
 - effects of route and schedule of administration on activity and toxicity



Goals of the Preclinical Safety Program II

- To identify potential target organs for toxicity related to the product
 - *In vitro* tissue binding and/or target antigen distribution studies may guide gross- and histopathology studies, which may guide subsequent safety pharmacology studies
 - Studies should define dose dependence, relationship to exposure, and potential reversibility

Goals of the Preclinical Safety Program III

- To identify appropriate serologic and immunologic parameters for monitoring the safety and efficacy of the product in human subjects
 - The quality, quantity, and relative contributions of cellular and humoral immunity (and complement) should be delineated
 - Correlation to outcomes should be sought



Goals of the Preclinical Safety Program IV

- To identify potential “at risk” populations for administration of the product
 - Such identification should be guided by the existing target organ toxicity data
 - Product administration in the context of animal models of disease (where available) may be of further utility

Goals of the Preclinical Safety Program V

- To help determine an acceptable risk/benefit ratio for human subjects
 - Risk/benefit will vary according to the indication and the intended target population
 - Evolving preclinical and clinical experience may shift the risk/benefit ratio during product development

Goals of the Preclinical Safety Program VI

- To help elucidate the mechanism of action of the product
 - An optimal dose regimen should consider the immunogenicity of the vaccine, the specific immune response desired, and the immune status of the study subjects

Types of Preclinical Studies I

- Local tolerance
- Pharmacodynamics
- Safety pharmacology
- Single and repeat dose toxicology

Types of Preclinical Studies II

- ADME
 - absorption, distribution, metabolism, and excretion
- Pharmacokinetics
- Carcinogenicity
- Genotoxicity
- Reproduction & developmental toxicology

Relevant ICH Guidance Documents

- M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
- S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
 - This document does not specifically cover cellular and gene therapies
- Several newer guidances in preparation



M3 for Tumor Vaccines I

- Toxicology should be performed in 2 relevant mammalian species (one non-rodent) with dose intensity \geq that anticipated in the clinical trials
- Where appropriate, ADME, local tolerance, and certain product class-specific studies should be performed prior to initiation of phase 1 trials

M3 for Tumor Vaccines II

- Reproductive and developmental toxicology should be conducted as appropriate for the population that is to be exposed
- Special considerations for pediatric administration include availability of
 - reproductive and developmental toxicology data
 - genotoxicity and carcinogenicity data
 - juvenile animal studies



M3 for Tumor Vaccines III

- Stepwise development is acceptable (“rolling toxicology” program)
- The safety evaluation may be considered on a product-specific basis if existing paradigms are inappropriate or irrelevant

S6 for Tumor Vaccines I

- Preclinical safety testing should consider:
 - Selection of relevant animal species
 - Age
 - Physiologic state (normal v disease model)
 - Delivery (dose, route, and regimen)
 - Stability of the test material under the conditions used

S6 for Tumor Vaccines II

- Route and frequency of administration should parallel as closely as possible that proposed for the clinical trial
- Exposure to the product should define NOEL, NOAEL, PEL, OBD, and MTD
- When appropriate, safety pharmacology can be incorporated into the design of toxicology studies

S6 for Tumor Vaccines III

- Study designs should include a delayed re-challenge cohort and recovery cohort for assessment of late toxicities and potential reversibility
- A flexible, science-based approach designed to address issues specific/unique to each product should be utilized for the preclinical safety evaluation

Major Safety Concerns for Tumor Vaccines

- Injection site reactions
- Systemic toxicity/pyrogenicity
- Hypersensitivity to vaccine components
- Cytokine release syndrome
- Induction of autoimmunity
 - Role of antigen specificity and tolerance
- Induction of disease

Major Limitations of Preclinical Studies

- Species specificity
- Difficulty in modeling long-term toxicities
- Difficulty in adequately assessing potential reversibility of toxicity
- Difficulty modeling study population
 - Age
 - Immunocompetence

Conclusions

- The preclinical program needs to address:
 - Safety and biologic activity of the product
 - Mechanism of action of the product
- Unique properties of individual products must be considered on a product-specific basis